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13. ABSTRACT ***(Maximum 200 Words)***

This project aims to identify potentially preventable environmental influences on breast and ovarian cancer by focusing on a population of women with genetically inherited predisposition to the disease. This study is an extension of our ongoing research into the genetics of breast and ovarian cancer among women of Jewish ancestry in the New York City area. The IDEA project focuses on female relatives of breast cancer patients with confirmed mutations in BRCA1 or BRCA2. Each relative provides a blood sample for mutation testing and completes an extensive questionnaire addressing epidemiologic factors in breast cancer risk. Not all women with inherited BRCA mutations develop breast or ovarian cancer, and among those who do, ages at cancer onset vary widely, even in families. As such, comparing the experiences and exposures of women with mutations who develop breast or ovarian cancer vs. women with the same mutations who remain cancer-free may identify factors that ameliorate or exacerbate risk in this group of very high-risk women. Risk factors identified among genetically predisposed women also may be generalized to women without inherited vulnerability to breast or ovarian cancer, since inherited cancer is virtually indistinguishable, clinically and biologically, from its noninherited counterpart.

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ENVIRONMENTAL AND LIFESTYLE INFLUENCES ON BREAST CANCER RISK: CLUES FROM WOMEN WITH INHERITED MUTATIONS IN BRCA1 AND BRCA2

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INTRODUCTION

Women with inherited disease-associated mutations in BRCA1 or BRCA2 have significantly elevated risks of breast cancer and of ovarian cancer. However, not all women with inherited BRCA1 or BRCA2 mutations develop breast or ovarian cancer, and among those who do, ages at cancer onset vary widely, even within the same family. If a woman with a BRCA1 or BRCA2 predisposing mutation remains free of breast and ovarian cancer for many years, it is possible that her status is due to chance, to modifying genes segregating in some families or to environmental factors that influence risk. In this project, we evaluate environmental and lifestyle factors that could influence penetrance of mutations in BRCA1 and BRCA2. It is possible that risk factors identified among genetically predisposed women may be generalized to women who have not inherited vulnerability to breast or ovarian cancer, because clinically and biologically, inherited cancer is virtually indistinguishable from its far more common, non-inherited counterpart.

BODY OF REPORT

Task 1. Send letters to eligible relatives explaining the study and inviting them to pre-test counseling.

Task 2. Provide pre-test counseling to relatives, administer informed consent and release forms for hospital records, obtain completed epidemiologic questionnaires and send blood samples to the University of Washington for mutation analysis.

Task 3. Maintain a database of contacts for participants and for those who decline participation after pre-test counseling.

By the end of the period covered by this report (Aug 31, 2000), 840 breast cancer patients entered the study as probands. Patients eligible to participate as probands are incident breast cancer patients of Jewish ancestry diagnosed at any of 10 cancer centers in the greater New York area: Albert Einstein Medical Center, Beth Israel Medical Center, Columbia Presbyterian Medical Center, Hackensack University Medical Center, Memorial Sloan-Kettering Cancer Center, New York University Medical Center, North Shore University Hospital, Stamford Hospital, Strang Cancer Prevention Center and White Plains Hospital Center.

Each patient eligible to participate was offered pre-test genetic counseling and testing for inherited predisposition due to any of three ancient BRCA1 and BRCA2 mutations (BRCA1 185delAG, BRCA1 5382insC, BRCA2 6174delT). Each eligible patient who chose to participate

provided information about her family history of breast cancer, completed the Environmental Factors Questionnaire and provided a blood sample for DNA isolation. Our study coordinator, board-certified Genetic Counselor Jessica Mandell, M.S., supervised completion of Tasks 1, 2 and 3 at each of the collaborating sites.

For each proband identified with a BRCA1 or BRCA2 mutation, all adult relatives, regardless of cancer history, were offered the opportunity to participate in the project. Jessica Mandell provided pre-test genetic counseling for each of these relatives. Each relative who agreed to participate completed the Environmental Factors Questionnaire and provided a blood sample. By the end date of the period covered by this report (Aug 31, 2000), 280 relatives from families with BRCA1 or BRCA2 mutations enrolled in the study.

Task 4. Genotype blood samples from participants for relevant mutations in BRCA1 and BRCA2.

In our laboratory at the University of Washington, BRCA1 and BRCA2 were genotyped for three founder mutations known to be common in the Jewish population. Frequencies of each mutation, by age of proband at diagnosis, are shown in Table 1.

Table 1. Frequency of ancient BRCA1 and BRCA2 mutations among probands in the NYBCS, by age at diagnosis of breast cancer.

Proband's age at diagnosis of breast cancer	Number of probands	BRCA1 185delAG	BRCA1 5382insC	BRCA2 6174delT	Any of 3	Proportion of probands with mutations
<35	31	5	6	3	14	0.45
35-39	59	4	5	8	17	0.29
40-44	108	9	1	9	19	0.18
45-49	158	10	1	3	14	0.09
50-54	145	2	5	3	10	0.07
55-59	107	4	2	2	8	0.07
60-64	76	0	1	0	1	0.01
65-69	69	1	0	0	1	0.01
70-74	52	0	0	1	1	0.02
75+	31	0	0	1	1	0.03
male	3	0	0	0	0	0.00
Total	840	35	21	30	86	0.102
Frequency		0.042	0.025	0.036	0.102	
Mean age dx		43.9	43.4	43.9		

The relationship between family history of breast cancer and the presence of mutations in the probands is shown in Table 2.

Table 2. Frequency of ancient BRCA1 and BRCA2 mutations among probands in the NYBCS, by family history of breast or ovarian cancer.

Relative with cancer	Number of probands	BRCA1 185delAG	BRCA1 5382insC	BRCA2 6174delT	Any of 3	Proportion of probands with mutations
All probands	840	35	21	30	86	0.10
Breast cancer						
Mother	197	15	8	6	29	0.15
Sister	83	5	2	5	12	0.14
Daughter	9	0	0	1	1	0.11
MGM or MA	182	10	8	3	21	0.12
PGM or PA	135	10	5	6	21	0.16
male relative	16	1	0	3	4	0.25
Ovarian cancer						
Mother	27	6	3	0	9	0.33
Sister	16	3	1	1	5	0.31
Daughter	3	1	0	0	1	0.33
MGM or MA	28	9	2	0	11	0.39
PGM or PA	27	4	0	2	6	0.22
No breast/ov ca among M, S, D, GM, A	350	6	8	12	26	0.07

GM=grandmother, A=aunt: maternal (M) or paternal (P)
*Probands may be in more than one category, depending on family history

Task 5. Report results of studies to patients as part of post-test genetic counseling.

Results of our genetic testing were reported to all probands in the context of post-test genetic counseling at their original cancer centers. Results were reported to each participating relative in the context of post-test genetic counseling by Jessica Mandell, at a time and place convenient for the relative. Medical referrals for relatives with BRCA1 or BRCA2 mutations were arranged by Ms. Mandell through local cancer centers.

Task 6. Enter responses from questionnaires for use in analysis.

This task is in progress by Ming Lee, biostatistics coordinator for the project at the University of Washington, for all 840 probands and 280 relatives.

Task 7. Carry out statistical analyses of associations of epidemiologic risk factors and breast cancer incidence among mutation carriers and (for comparison) among relatives not carrying mutations.

Evaluation of environmental exposures among genetically predisposed relatives is an analysis of gene-environment interaction in that all individuals in the analysis carry a predisposing mutation. A powerful approach is to compare cumulative incidence of breast cancer by age among female mutation carriers with vs. without a specified risk factor. The project is enrolling participants at the rate expected, so by the end of the study, sample size will be adequate for these comparisons. In this reporting period, software was developed for the following analyses:

Lifetime risk of breast cancer, by mutation status
Lifetime risk of ovarian cancer, by mutation status
Association of age at menarche, age at first birth and age at menopause with breast cancer incidence among women with mutations
Association of breastfeeding with breast cancer incidence among women with mutations
Association of oral contraceptive use with breast cancer incidence among women with mutations
Association of hormone replacement therapy with breast cancer incidence among women with mutations
Association of exposure to cigarette smoke (either smoking history or indirect exposure) with breast cancer incidence among women with mutations
Association of alcohol consumption with breast cancer incidence among women with mutations
Association of medical x-ray exposure with breast cancer incidence among women with mutations
Association of occupational exposure to radiation with breast cancer incidence among women with mutations
Association of occupational or household exposure to pesticides with breast cancer incidence among women with mutations

KEY RESEARCH ACCOMPLISHMENTS

- 840 incident breast cancer patients of Jewish ancestry have enrolled in our study, received genetic counseling, completed the Environmental Factors questionnaire and been genotyped for the three ancient Jewish BRCA1 and BRCA2 mutations.

- Genotypes have been reported back to all participants requesting this information in the context of post-test counseling.

- Among our probands, 86 carry one of the three ancient BRCA mutations. Mutations are more frequent among probands with younger ages at diagnosis.

- 280 relatives from these 86 families with BRCA1 or BRCA2 mutations have been enrolled and genotyped.

- Environmental Factors Questionnaires of probands and their relatives have been collected and are being encoded for statistical analysis. Software for statistical analyses has been developed.

REPORTABLE OUTCOMES

No publications have been generated from the study as of August 31, 2000.

CONCLUSIONS

Evaluation of environmental effects which might influence risk of breast cancer are ongoing.